Postintervention Effects of Varying Treatment Arms on Glycemic Failure and β-Cell Function in the TODAY Trial

*The TODAY Study Group**

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OBJECTIVE

The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) trial demonstrated that glycemic failure rates were significantly lower in youth randomized to metformin plus rosiglitazone treatment than in youth randomized to metformin alone or metformin plus intensive lifestyle intervention. At the end of the study, rosiglitazone was permanently discontinued, and routine diabetes care resumed. Herein, we report postintervention glycemic failure rates in TODAY participants over an additional 36 months of follow-up for the three original treatment arms and describe insulin sensitivity and β-cell function outcomes.

RESEARCH DESIGN AND METHODS

A total of 699 participants were randomized during TODAY, of whom 572 enrolled in the TODAY2 observational follow-up. Glycemic failure was defined as HbA_{1c} ≥8% over a 6-month period, inability to wean from temporary insulin therapy within 3 months after acute metabolic decompensation during TODAY, or sustained HbA_{1c} ≥8% over two consecutive visits during TODAY2. Oral glucose tolerance tests were conducted, and insulin sensitivity, insulinogenic index, and oral disposition index were calculated.

RESULTS

During the 36 months of TODAY2, glycemic failure rates did not differ among participants by original treatment group assignment. Insulin sensitivity and β-cell function deteriorated rapidly during the 36 months of TODAY2 routine diabetes care but did not differ by treatment group assignment.

CONCLUSIONS

The added benefit of preventing glycemic failure by using rosiglitazone as a second agent in youth-onset type 2 diabetes did not persist after its discontinuation. More work is needed to address this rapid progression to avoid long-term diabetes complications.

Youth-onset type 2 diabetes has increased in prevalence over the last several decades, yet there are still only limited medications approved for treatment (1–3). The Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) multicenter randomized clinical trial demonstrated that combined treatment with metformin plus rosiglitazone preserved glycemic control (defined as a persistent HbA_{1c} <8% without metabolic decompensation or a persistent insulin requirement) more effectively than

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**A complete list of the TODAY Study Group members can be found in the supplementary material.*

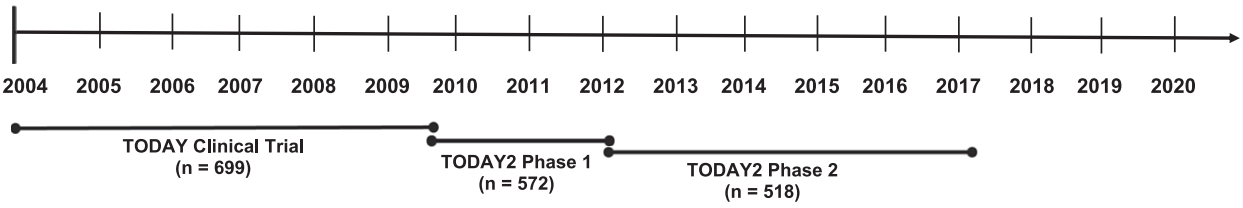

Figure 1—TODAY and TODAY2 flow diagram.

monotherapy with metformin (4). Participants in the metformin plus lifestyle intervention arm did not differ in glycemic control compared with the other two treatment arms. Sex and racial differences regarding glycemic control were also noted in the initial TODAY results. Metformin plus rosiglitazone was more effective at preventing glycemic failure in girls than in boys. Non-Hispanic Blacks had the highest rates of overall glycemic failure, followed by Hispanics and non-Hispanic Whites.

The TODAY trial reported that both insulin sensitivity and insulin secretion relative to insulin sensitivity (measured by oral disposition index [oDI]) improved in the metformin plus rosiglitazone arm in the first 6 months compared with the two other treatment groups (5). After 6 months, insulin sensitivity and oDI fell at similar rates in all three treatment groups, but the initial improvement in the metformin plus rosiglitazone group resulted in a long-term improvement in both measures compared with the two other treatment arms tested during TODAY. Insulinogenic index, which correlates with the first-phase insulin response in hyperglycemic clamp studies (6), declined steadily during TODAY, particularly in participants with glycemic failure, irrespective of treatment arm (5). Insulinogenic index measured at randomization in TODAY was a good predictor of glycemic failure in TODAY participants (7).

At the end of the TODAY intervention phase, TODAY2 began a 36-month observational follow-up phase. Rosiglitazone was permanently discontinued, and participants received standard diabetes care without assignment to a specific treatment arm. Herein, we aim to evaluate whether the initial treatment arm differences in glycemic failure, insulin sensitivity, and β-cell function persisted after discontinuation of the randomized interventions.

RESEARCH DESIGN AND METHODS

Study Design

The study design and detailed methods of the TODAY trial (2004–2011) (clinical trial reg. no. NCT00081328, ClinicalTrials.gov) have previously been published (Fig. 1). Briefly, the trial consisted of a screening phase, run-in phase, and randomized clinical trial (4,8,9). During the run-in phase, children/adolescents (ages 10–17 years) absent of pancreatic autoantibodies and diagnosed with type 2 diabetes for <2 years (mean duration 7.8 months), were weaned to metformin monotherapy maintaining an HbA_{1c} <8% for a minimum of 2 months (9). A total of 699 participants were then randomized into one of three treatment arms: metformin alone, metformin plus an intensive lifestyle intervention, and metformin plus rosiglitazone (4) and followed for an average of 3.86 years (4). The primary outcome was time to glycemic failure, defined as an HbA_{1c} ≥8% over a 6-month period or inability to wean from temporary insulin therapy within 3 months after acute metabolic decompensation. Oral glucose tolerance tests (OGTTs) were performed at randomization, at 6 and 24 months, and annually thereafter.

In 2011, 572 TODAY participants enrolled in the TODAY2 follow-up study, which was conducted in two phases (Fig. 1). During TODAY2 Phase 1 (2011–2014), rosiglitazone was permanently discontinued, and participants were transitioned to nonblinded, nonrandomized, standard diabetes care. Participants attended quarterly and annual visits receiving metformin monotherapy at the same dose they were taking at the end of TODAY. Add-on insulin therapy was continued or started in participants who had metabolic decompensation (defined as blood glucose levels >300 mg/dL with other clinical symptoms) or who had HbA_{1c} ≥8%. All medications were dispensed by study staff, and participants were treated and monitored for 36 months. During TODAY2 Phase 1 observational follow-up, glycemic failure was defined as sustained HbA_{1c} ≥8% over two consecutive visits.

Assays and Calculations

All laboratory assays were performed at the TODAY central laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle, WA). Specific laboratory assays and calculations have previously been described in detail (5,10). Insulin sensitivity was calculated as 1/fasting insulin (1/IF), and the insulinogenic index ($\Delta I_{30-0}/\Delta G_{30-0}$) was calculated as the ratio of the incremental insulin (I) and glucose (G) responses over the first 30 min of the OGTT (10). The oDI measures β-cell function relative to insulin sensitivity and was calculated by multiplication of insulin sensitivity by the insulinogenic index ($1/IF \times \Delta I_{30-0}/\Delta G_{30-0}$) (10). Per protocol, OGTTs were performed, but stimulated insulin was not collected for participants with glycemic failure or in whom insulin therapy had already started; therefore, for this analysis, we used OGTT measurements taken prior to participants reaching the primary outcome. Treatment group differences in the above calculated measures over time may be influenced by the successive removal of participants due to treatment failure.

Statistical Analyses

All randomized TODAY participants were included in the analysis with the exception of 22 participants subsequently identified with genetic mutations consistent with maturity-onset diabetes of the young (11). Treatment group differences among the 677 participants were evaluated during TODAY only, TODAY2 Phase 1, and TODAY + TODAY2 Phase 1 combined (a total of 96 months: 60 months during TODAY plus 36 months during TODAY2 Phase 1). Analyses were also conducted according to sex and race/ethnicity.

Time-to-event analyses were used to evaluate treatment group differences in glycemic failure during TODAY2 Phase 1, as well as over the TODAY + TODAY2 Phase 1 combined follow-up. Due to staggered entry at randomization, participants had on average 3.8 years of follow-up during TODAY and 7.0 years of follow-up during the combined TODAY + TODAY2 Phase 1 study. For participants

who had treatment failure, the time contributed was from the baseline visit in TODAY to time of failure. For participants who did not have treatment failure, the time contributed was from the baseline visit in TODAY to the last visit in TODAY2 Phase 1, unless the participant withdrew or did not return for follow-up ($n = 86$), underwent bariatric surgery ($n = 13$), or chose to take insulin ($n = 12$) despite not having reached the study end point. A log-logistic distribution was specified for time to failure. The trial was powered for three pairwise comparisons among treatment groups for the primary outcome, each at a significance level of 0.0167 (0.05/3).

Longitudinal linear models were used to estimate mean levels of the β-cell function parameters within groups during TODAY2 Phase 1, as well as over the combined 96-month follow-up period. Analyses of the reciprocal of fasting insulin, insulinogenic index, and oDI used the natural log transformation to better approximate a normal distribution. Data in the figures are presented as baseline adjusted geometric means ± SE asymmetric limits (obtained as exp[mean ± SE of the log values]). All figures are adjusted for concurrent BMI. Models evaluating time since randomization were adjusted for the baseline value of the β-cell function parameter, while those restricted to just the TODAY2 Phase 1 period were adjusted for the TODAY end-of-study value.

RESULTS

Glycemic Failure

At the beginning of TODAY2 Phase 1, there were 102 participants who had not reached the primary outcome in the former metformin plus rosiglitazone treatment arm compared with 84 and 88 participants in the metformin alone and metformin plus lifestyle arms, respectively (Table 1). During TODAY2 Phase 1, participants had glycemic failure at an overall event rate of 17.3 per 100 patient-years. In this 36-month period, the rate of glycemic failure did not differ among participants who were previously assigned to any of the three TODAY treatment arms (Fig. 2). By the end of the 96 months of follow-up (TODAY + TODAY2 Phase1), 173 total participants remained free of glycemic failure, representing 25.6% of the original cohort (Supplementary Fig. 1). There were no statistically significant differences by sex or race/ethnicity.

Insulin Sensitivity and β-Cell Function

There were no differences in insulin sensitivity, insulinogenic index, or oDI among any of the original treatment groups during TODAY2 Phase 1 (Fig. 3*A*–*C*). At the end of TODAY, insulin sensitivity was similar in all participants, regardless of prior assigned TODAY treatment arm. For 2 years, insulin sensitivity remained unchanged and similar among groups; however, by the end of TODAY2 Phase 1, it appeared to rise in all three groups ($P < 0.0001$ vs. 12 months and 0.0002 vs. 24 months) (Fig. 3*A*). However, the sample size of participants who had not yet met glycemic failure by the end of TODAY2 Phase 1 was small ($n = 80$).

CONCLUSIONS

Type 2 diabetes diagnosed in children and adolescents is an aggressive disease associated with faster rates of glycemic failure (4,12), β-cell failure (5,13,14), and diabetes-related vascular complications (15–17) than seen in adults with comparable durations of disease (14,18). The TODAY intervention trial, which began in 2003, tested the efficacy of three treatments arms (measured by time to glycemic failure) in participants with youth-onset type 2 diabetes (4). Metformin was chosen because it was the only oral medication approved for treating type 2 diabetes in youth, whereas rosiglitazone would presumably aid in insulin sensitization and β-cell function. Initial results from the Troglitazone in Prevention of Diabetes (TRIPOD) study in 2002 showed that type 2 diabetes could be prevented by use of troglitazone in high-risk adult Hispanic women with a history of gestational diabetes mellitus with preservation of β-cell function (19). At the time of the design of the TODAY trial (2001–2003), it was not clear whether or for how long the protective effect of thiazolidinediones (TZDs) would last. Other studies evaluating the effect of TZDs in adults with type 2 diabetes were published after the TODAY trial was underway (20–22). TZDs such as rosiglitazone were known to have side effects in adults during the design of the initial TODAY study, including fluid retention/edema, congestive heart failure, anemia, and weight gain. The risk-to-benefit ratio was deemed low in this pediatric population at the onset of the study. After the initial TODAY trial was well underway, additional concerns were raised in the adult literature, including an increased risk of myocardial infarction (23), bone fractures (24), and macular edema (25), so participants were screened for these side effects during TODAY and TODAY2. Rosiglitazone therapy was discontinued as per the original protocol at the end of TODAY, as it was not labeled for use in pediatric patients with diabetes.

During TODAY, the metformin plus rosiglitazone arm proved to have lower rates of glycemic failure (39%) compared with the other two treatment arms: metformin alone (52%) and metformin plus intensive lifestyle intervention (47%) (4). Overall, 45.6% of TODAY participants lost glycemic control, with a median time to treatment failure of 11.5 months (4). The A Diabetes Outcome Progression Trial (ADOPT) in adults analyzed the efficacy of metformin, rosiglitazone, or glyburide as first-line treatment of adults with recently diagnosed type 2 diabetes (12). In this study, glycemic failure was defined as consecutive fasting glucose levels of >180 mg/dL, and rates were considerably lower than those seen in TODAY: 15% in participants taking rosiglitazone, 21% in those taking metformin, and 34% in the glyburide arm after 5 years of monotherapy (12).

The TODAY2 Phase 1 investigated whether prior use of metformin plus rosiglitazone offered a continued protective effect against glycemic failure even after rosiglitazone had been discontinued. Our results show that there is no protective "legacy effect" from prior use of rosiglitazone in teens with type 2 diabetes. The protective effect of rosiglitazone was only present while patients were actively taking it and did not persist after it was discontinued. These results are similar to what was reported in Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) in adults with prediabetes who, while receiving rosiglitazone for 3 years, were more likely to have normoglycemia, were less likely to progress to diabetes, and had improved β-cell function (26). However, 1.5 years after discontinuation of rosiglitazone, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Ongoing Follow-up (DREAM On) failed to show a difference in the rate of incidence of diabetes between patients formerly on rosiglitazone and those who had been taking placebo (27).

Table 1—Number of participants who reached primary outcome during TODAY and TODAY2 Phase 1

	Overall	Met only	Met + lifestyle	Met + Rosi
TODAY				
n participants	677	226	224	227
Glycemic failure during TODAY	309 (45.6)	117 (51.8)	104 (46.4)	88 (38.8)
Time to failure (months)	11.8 (4.6, 23.9)	10.2 (3.8, 22.5)	11.9 (5.5, 24.8)	12.1 (6.2, 25.3)
Event rate per 100 patient-years	17.9	21.6	17.8	14.7
n participants at the end of TODAY who had not reached primary outcome	368	109	120	139
TODAY2 Phase 1				
n participants who had not reached primary outcome	274*	84	88	102
Glycemic failure during TODAY2 Phase 1	101 (36.9)	31 (36.9)	29 (33.0)	41 (40.2)
Time to failure (months)	11.7 (3.7, 23.9)	14.6 (6.0, 21.9)	11.3 (5.6, 19.1)	9.7 (3.1, 27.6)
Event rate per 100 patient-years	17.3	18.8	15.1	18.0
n participants at the end of TODAY Phase 1 who had not reached primary outcome	173	53	59	61
TODAY + TODAY2 Phase 1, combined				
n participants	677	226	224	227
Glycemic failure during TODAY + TODAY2 Phase 1	410 (60.6)	148 (65.5)	133 (59.4)	129 (56.8)
Time to failure (months)	18.0 (6.6, 44.7)	14.9 (5.7, 37.7)	17.9 (6.5, 40.2)	23.9 (9.9, 50.9)
Event rate per 100 patient-years	17.8	21.0	17.2	15.6

Data are *N* (%) or median (quartile 1, quartile 3) unless otherwise indicated. Met, metformin; Rosi, rosiglitazone. *$n = 368$ participants at the end of TODAY who had not reach primary outcome minus $n = 94$ who were censored at the end of TODAY: $n = 86$ who never enrolled in TODAY2, $n = 5$ who chose to remain on insulin during TODAY, and $n = 3$ who had bariatric surgery during TODAY.

β-cell function appeared to deteriorate over the first 3 years of TODAY2, irrespective of prior TODAY treatment arm, at a faster rate than that seen in adults with type 2 diabetes (12). The persistent decline in both first-phase insulin response (measured by insulinogenic index) and insulin secretion (measured by oDI) explains the profound loss of glycemic failure in these subjects. Our prior results demonstrated that while insulin sensitivity improved in the first 6 months of the TODAY trial for those in the metformin combined with rosiglitazone arm, it subsequently fell and was similar in all three groups (5). However, insulin sensitivity appeared to rise in all active participants who had not reached the primary outcome toward the end of TODAY2 Phase 1. This late rise in insulin sensitivity may be a consequence of the small number of remaining subjects ($n = 80$) without glycemic failure or could be explained by the postpuberty reduction in insulin resistance, since the average age of participants at the end of TODAY 2 Phase 1 was 21 years. Nevertheless, this improvement in insulin sensitivity did not coincide with preservation of β-cell function.

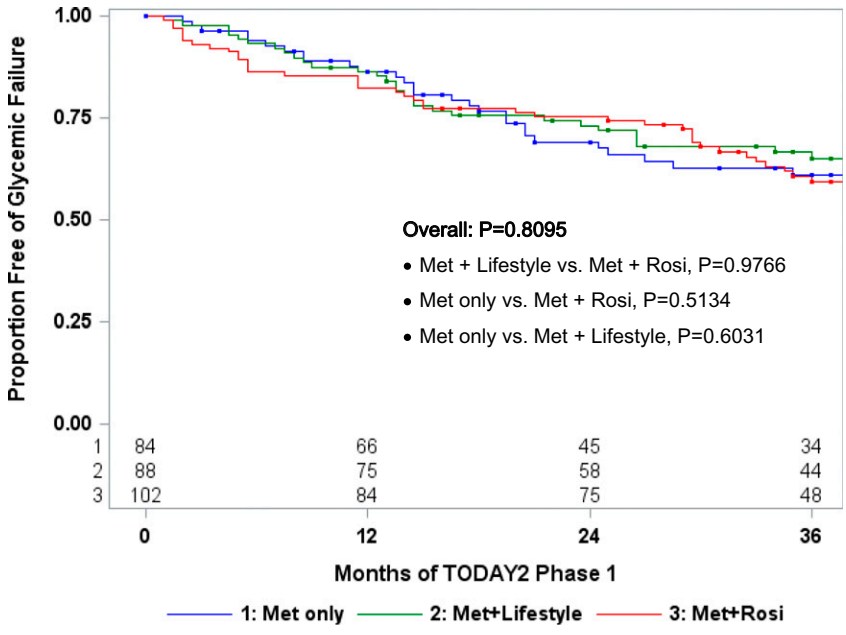

Figure 2—Primary outcome results during TODAY2 Phase 1. For participants who had treatment failure, the time contributed was from the baseline visit to time of failure. For participants who did not have treatment failure, the time contributed was from the baseline visit to the last visit in most cases, unless the participant withdrew or did not return for follow-up ($n = 86$), underwent bariatric surgery ($n = 13$), or chose to take insulin ($n = 12$) despite not having reached the study end point. Met, metformin; Rosi, rosiglitazone.

These results are similar to those reported by the Restoring Insulin Secretion (RISE) Consortium (28). RISE participants were youth and adults with obesity and either recent-onset prediabetes or type 2 diabetes who were randomized to receive either glargine insulin followed by metformin or metformin alone (29). In the youth participants, β-cell function, measured by hyperglycemic clamp, worsened in both treatment groups and continued to deteriorate after treatment was withdrawn (19). Conversely, the adult RISE participants showed stable or improved β-cell function while on treatment, but this improved β-cell function was not

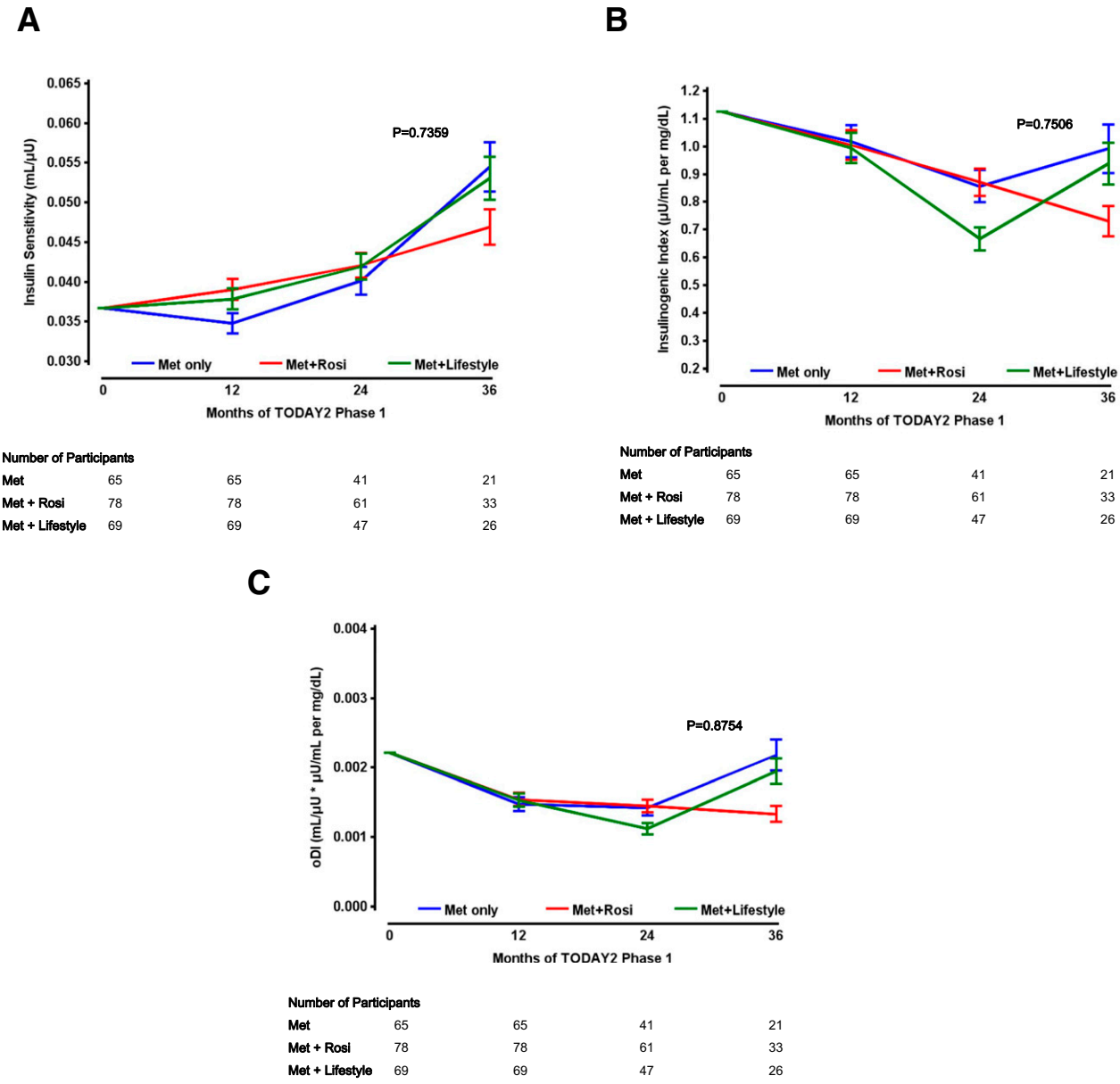

Figure 3—OGTT-derived measures of insulin sensitivity (*A*), insulinogenic index (*B*), and oDI (*C*) in the three treatment groups during TODAY2 Phase 1, analyzed with use of log-transformed values. Data are expressed as geometric mean ± SE, with adjustment for concurrent BMI value as well as the TODAY closeout value of the β-cell function parameter. The *P* value refers to the overall effect of treatment group assignment in the longitudinal models. Met, metformin; Rosi, rosiglitazone.

sustained after treatment was removed (19).

A strength of the current study is that it provides longitudinal data on the TODAY cohort, the largest group of well-characterized participants with youth-onset type 2 diabetes in the literature thus far. One limitation is that, although OGTTs were performed, stimulated insulin was not collected for participants after glycemic failure. Therefore, data on insulin sensitivity, β-cell function, and oDI were available on fewer participants in TODAY2 because many had already reached the primary outcome. Another limitation of the study was that physical activity was not systematically evaluated in TODAY2.

In summary, in TODAY participants, prior use of rosiglitazone, which initially resulted in lower glycemic failure rates, did not protect against glycemic failure after it was discontinued. Moreover, there were no differences in insulin sensitivity and β-cell function among TODAY2 participants based on their TODAY treatment group assignment. More studies are needed to identify more effective methods of treating youth with type 2 diabetes to improve glycemic control and halt the rapid progression of β-cell decline with the ultimate goal of preventing diabetes-related complications.

APPENDIX

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Author Contributions. R.G. wrote the manuscript. B.H.B. conducted the statistical analyses and wrote sections of the manuscript. L.E.L.K., N.H.W., J.B.T., M.E.G., S.C., S.M., K.J.N., and S.A. wrote sections of the manuscript and reviewed, and edited the manuscript. B.H.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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